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14. ABSTRACT

In a randomized, double-blind, sham-controlled study, we have demonstrated that tDCS of the motor and frontal cortex is safe and improves bradykinesia for a longer time period and also gait in patients with moderate PD. This improvement beyond optimal dopaminergic treatment suggests efficacy also on non-dopaminergic deficits and highlights its usefulness as an adjunctive therapeutic tool in PD. This study has been terminated (project A-13864.1: "Transcranial Electrical Polarization for the Treatment of Bradykinesia and Rigidity in Patients with Parkinson's Disease").

The rTMS has shown promising results in treating PD, but the best values for rTMS parameters are not established. Since 50 Hz rTMS may be superior to ≤ 25 Hz rTMS investigated so far and exceeds current safety limits, the objective of this second project (A-13864.2 "Safety Study of the Super Rapid Transcranial Magnetic Stimulation in Patients with Parkinson's Disease") was to determine if 50 Hz rTMS could be delivered safely in PD patients. The results suggest that 50 Hz rTMS at an intensity of 90% RMT for 2 sec are safe in patients with PD. This study is being terminated.

In the third project (A-13864.3 "Super Rapid Transcranial Magnetic Stimulation for the Treatment of Bradykinesia and Rigidity in Patients with Parkinson's Disease"), we are investigating safety and efficacy of 50 Hz rTMS for the treatment of PD using a randomized, double-blind, sham-controlled study design.

15. SUBJECT TERMS
None provided

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Introduction

Drug treatments for akinesia and rigidity in PD currently revolve around dopamine containing medications. PD is typically easy to treat early in the disease, but later the response declines and complications develop. Postural instability associated with gait disorder is usually a very disabling, less treatable manifestation of PD, and it represents a major contributing factor in progression from mild bilateral disease to wheelchair confinement (Paulson, Stern, 1997).

Recent studies have demonstrated that anodal TEP (application of DC current) over the primary motor cortex (M1) produced sustained cortical excitability elevation measured by the amplitude of MEPs elicited by M1 TMS (Nitsche & Paulus 2000; 2001). Reversed polarity of the DC application resulted in opposite change of cortical excitability. fMRI demonstrated that cathodal polarization resulted in a global decrease of the mean number of activated pixels in M1 during sequential finger opposition test, while anodal polarization increased this number (Baudewig et al. 2001). Significant visual perception loss (static and dynamic contrast sensitivity) was found after 7 minutes of cathodal polarization of the occipital cortex (Antal et al. 2001). The duration of the described effects is in the minutes range. Such a change of cortical neuron excitability was also found several decades ago in experimental animal studies with intracerebral electrodes and was called "a dominant focus," highly reactive to external stimuli involved in the process of conditioning (Rusinov 1973; 1981). Intriguingly, the behavioral effects reported in animals may persist for weeks (Hori & Yamaguchi 1975) and may occur with stimulation at microampere current intensity (Lu et al. 1994). Polarization using 1–4 mA DC current, similar to the current in this application, was accompanied by EEG amplitude increases in animals and in humans (Vartanian et al. 1978; Lomarev 1989) that may be interpreted as an effect on postsynaptic processes, considering postsynaptic potential summation to be a main source of scalp EEG. TEP ultrastructural presynaptic effects ("condensation of synaptic vesicles in the center of presynaptic terminals, increase of electron microscope density, lightening of axonal terminals") were also revealed in the prefrontal and temporal cortex of experimental animals (Akimova & Novikova 1978; Vartanian et al. 1978). The possibility of modulation of cortical excitability by TEP may be of some interest for the development of therapeutic interventions in patients with PD. This is of particular interest, taking into consideration hypoactivity of the supplementary motor area (SMA) in PD demonstrated in a variety of experimental approaches. fMRI (Tada 1998) and blood-flow PET studies (Playford et al. 1992; Jahanashahi et al. 1995) have revealed less SMA, putamen, anterior cingulate, and medial and dorsolateral prefrontal cortex activation in PD patients compared to matched controls. These hypoactive areas have been partially improved by apomorphine (Jenkins et al. 1992; Rascol et al. 1992). In one study, SMA hypoactivity was associated with compensatory overactivity of the lateral premotor and parietal cortex (Brooks 1999). DBS of the STN enhanced movement-related activation in SMA, premotor cortex, and decreased M1 activation at rest (Limousin et al. 1997; Ceballos-Baumann et al. 1999) and influenced prefrontal BOLD activation (Sakatani et al. 1999).
SMA hypoactivity in PD was further confirmed electrophysiologically. A positive correlation was revealed between SMA hypoactivity measured by PET rCBF and early Bereitschaftspotential (BP) component amplitude in PD patients during self-initiated movements (Jahanashahi et al. 1995). Several authors confirmed reduction of BP components in PD (Dick et al. 1989; Tarkka et al. 1990; Ikeda et al. 1997). L-DOPA increased the early part of BP and the peak negativity, and dopamine antagonists decreased the amplitude in healthy controls (Dick et al. 1987).

TEP behavioral and electrophysiological effects in PD were studied in a pilot open research study in the Institute of the Human Brain of the Russian Academy of Sciences in St. Petersburg, Russia, resulting in the development of the method of treatment of PD by TEP (Lomarev et al. 1991). The study used the same TEP parameters as the current protocol in 42 patients with akinetic rigid form of PD, most of whom were also taking L-DOPA containing drugs (precursors of dopamine). In that pilot open design study, TEP improved bradykinesia and rigidity but not tremor in the majority of cases. This study used EEG and other electrophysiological methods to develop safe and effective TEP parameters and regimens (Lomarev 1989; 1996; Lomarev et al. 1991; 1993). Safe TEP parameters were found, which did not cause any significant side effects. They were characterized in terms of the most intense current, the longest session duration and the maximum number of sessions per week. Safety criteria were based in part on EEG recordings. Safe parameters did not provoke epileptiform or synchronized paroxysmal EEG activity in patients with PD. TEP was effective when applied within 1–2 hours after the last L-DOPA medication. This suggests a synergistic effect of the TEP and L-DOPA. The reduction of rigidity correlated with DC-potential positive shift in the records from the scalp (over the primary motor cortex, $T_{3,4}$, $P_{3,4}$). Decrease of evoked potential amplitude produced by muscle stretch was also recorded from the same leads. Early component reduction was more pronounced in the leads from the electrodes over the upper part of the precentral gyrus, rather than parietal or temporal areas. All these phenomena may be interpreted as an indicator of the suppression of transcortical proprioceptive reflexes after the TEP.

To evaluate the TEP motor effects we utilized a set of sequential movement tests in different joints and rigidity measurements. These revealed a cumulative therapeutic effect over the series of TEP sessions when scores obtained before each session were compared to initial scores (Figure 1). The increment of improvement at each session gradually diminishes during the course of treatment implying either that the brain adapts to TEP or the benefit reaches a ceiling (Figure 2). Table 2 shows a relative improvement (percentage) of the bradykinesia (time of the test execution) and rigidity scores over the course of TEP treatment. The clinical efficacy of this method was evaluated in an open study only. The current proposal attempts to replicate this work using double-blind design and to study the possible long-lasting TEP therapeutic effect.

TMS is a tool that allows non-invasive stimulation of the cerebral cortex. Many researchers have used TMS to understand PD pathophysiology, but only a few researchers have used it for therapeutic trials. In an initial study of drug-free PD patients who received repetitive TMS (rTMS) applied to the primary motor areas contralateral to their performing hand, the time that they took to complete the Grooved Pegboard Test was shortened (Pascual-Leone et al., 1994a). However, these results were not reproducible (Ghabra et al., 1999). Single-pulse focal TMS shortened the simple reaction time in PD patients (Pascual-Leone et al., 1994b). In a different PD study, rTMS at 1 Hz frequency for 15 minutes increased the velocity of finger tapping (Sommer et al., 1998). Siebner et al. (1999, 2000) found that 5 Hz rTMS over the motor cortex improved ballistic movements for 20 minutes and decreased contralateral arm motor scores 1 hour after the TMS session. While some of these studies are encouraging, the cumulative effects of rTMS were not studied, and it is unclear whether it may have any long-lasting therapeutic effects (weeks or months) in persons with PD who are receiving optimal available therapy. Interestingly, recent studies with low-frequency rTMS using large circular coils over the vertex or dorsolateral prefrontal cortex (DLPC) in patients receiving levodopa/carbidopa reported a relatively long-lasting therapeutic effect (Mally, Stone, 1999; Shimamoto et al., 2001). The reasons for selecting specific rTMS frequencies and targets in these studies are unclear. The synergistic effect of rTMS and L-DOPA might be assumed, however, based on these data. Prefrontal rTMS with a circular coil increases dopamine release in the caudate nucleus of healthy humans (Strafella et al., 2002). rTMS also increased dopamine concentration in rat striatum and hippocampus, and decreased it in the prefrontal cortex (Belmaker and Grisaru, 1998). Long-lasting (months) improvement of Parkinsonian symptoms and increased cerebrospinal fluid (CSF) monoaminergic metabolites were also found after electroconvulsive (ECT) in patients who were receiving L-DOPA medication, further supporting the synergistic assumption (Balldin et al., 1982, Fall et al., 1995). Concentration of dopamine and its metabolites in the prefrontal cortex were increased because of the ECT (Yoshida et al., 1998). "Maintenance" ECT has been proposed to treat PD (Aarsland et al., 1997; Fall et al., 1995, 1999; Granerus, 1999).

The possibility of modulating cortical excitability by srTMS may be helpful for developing therapeutic interventions in PD patients. fMRI revealed that rTMS of the primary motor cortex (M1) indirectly, transynaptically activates SMA in healthy volunteers (Lomarev et al., 2000, 2002; Baudewig et al., 2001). 10 Hz at 110% MT SMA stimulation in drug-free PD patients worsened their performance in the spiral drawing test (Boylan, et al, 2001); probably as a result of temporarily blocking this area essential for the execution of the test. This effect persisted for 30-45 min. The authors also noted that the worsening of the test may persist up to the beginning of the next session (mean interval between the sessions was 1.6 weeks). This was not statistically significant. Parkinsonian symptoms are highly dependent on the time of the most recent L-DOPA or dopamine agonist medication before testing. The paper does not state the time of rTMS or the testing of motor functions with respect to L-DOPA medication and whether it was the same between first and retesting, nor whether it was the same in the real TMS and placebo groups. We are not going to do rTMS of the SMA. The best rTMS frequency for therapeutic intervention in PD is unclear. With high-frequency deep brain stimulation (DBS, >100Hz) of subthalamic nucleus (STN), globus pallidum (GP) was found to be more effective in patients with PD (Benabid et al., 1991; Pollak et al., 1993; Moro et al., 2002). A recent study has shown increasing therapeutic benefits by increasing stimulation frequency (Rizzone et al., 2001). Relatively high frequency (up to 50 Hz) motor cortex stimulation was used to treat pain (Tsubokawa et al., 1993; Saitoh et al., 2000). Now we may reach this frequency with rTMS. Therapeutic effects of this rTMS frequency (srTMS) have never been tested before in PD patients. 25 Hz rTMS improved gait and bradykinesia in PD patients in a placebo controlled study (Lomarev et al, 2006)."

The 50 Hz rTMS frequency proposed here is in a range currently out of established guidelines since such high frequencies have not been investigated (Wassermann, 1998, 2001). Thus, we initially propose a Phase I study that will include testing the safety of 50 Hz rTMS with different intensities and train durations. The M1 projection of the hand muscles has the lowest motor evoked potential (MEP) threshold (Wassermann, 1992); therefore, the 50 Hz rTMS safety limit (SL) established for the abductor pollicis brevis (APB) M1, the highly excitable brain area, may be used as an SL for 50 Hz rTMS for the other cortical structures.

Body

In the first project, a randomized, double-blind, sham-controlled study, we have demonstrated that tDCS of the motor and frontal cortex is safe and improves bradykinesia for a longer time period and also gait in patients with moderate PD. This improvement beyond optimal dopaminergic treatment suggests efficacy also on non-dopaminergic deficits and highlights its usefulness as an adjunctive therapeutic tool in PD. This study has been terminated (project A-13864.1: "Transcranial Electrical Polarization for the Treatment of Bradykinesia and Rigidity in Patients with Parkinson's Disease").

The rTMS has shown promising results in treating PD, but the best values for rTMS parameters are not established. Since 50 Hz rTMS may be superior to ≤ 25 Hz rTMS investigated so far and exceeds current safety limits, the objective of this second project (A-13864.2 "Safety Study of the Super Rapid Transcranial Magnetic Stimulation in Patients with Parkinson's Disease") was to determine if 50 Hz rTMS could be delivered safely in PD patients. The results suggest that 50 Hz rTMS at an intensity of 90% RMT for 2 sec are safe in patients with PD. This study is being terminated.

In the third project (A-13864.3 "Super Rapid (50 Hz) Transcranial Magnetic Stimulation for the Treatment of Bradykinesia and Rigidity in Patients with Parkinson's Disease"), we are investigating safety and efficacy of 50 Hz rTMS for the treatment of PD using a randomized, double-blind, sham-controlled study design.

Key Research Accomplishments and Reportable Outcomes

Multi-channel EMG showed no signs of increased time-locked EMG activity including correlates of the spread of excitation and after-discharges, or increased M1 excitability in 9 patients. A PD patient with bi-temporal spikes in the pre-testing EEG had clinical and EMG correlates of spread of excitation at 90% RMT, but no seizure activity. Pre- and post-50 Hz assessment showed no changes. No adverse events were observed. 50 Hz rTMS was well tolerated except by one patient who wished to terminate the study due to facial muscle stimulation. These findings were published:

BENNINGER D.H., LOMAREV M., WASSERMANN E., LOPEZ G., FASANO R., HOUDAYER E., DANG N., HALLETT M.
Safety study of 50 Hz repetitive transcranial magnetic stimulation in patients with Parkinson's disease. *Clinical Neurophysioogyl.* 2009 Apr;120(4):809-15.
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Twenty-five PD patients were investigated, 13 receiving tDCS and 12 sham stimulation. TDCS improved gait by some measures for a short time and improved bradykinesia in both the on- and off-states for longer than 3 months. Changes in UPDRS, reaction time, physical and mental well-being, and self-assessed mobility did not differ between tDCS and sham intervention. These findings were published:

BENNINGER D.H., LOMAREV M., LOPEZ G., WASSERMANN E.M., LI X., CONSIDINE E., HALLETT M.
Transcranial direct current stimulation in the treatment for Parkinson's disease.
Journal of Neurology, Neurosurgery and Psychiatry 2010;81:1105-1111
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In the meantime, we completed the recruitment of 26 patients for the third project "Super Rapid (50 Hz) Transcranial Magnetic Stimulation for the Treatment of Bradykinesia and Rigidity in Patients with Parkinson's Disease" which we're currently analyzing.

Conclusions

The results suggest that 50 Hz rTMS at an intensity of 90% RMT for 2 sec appears safe in patients with PD, but caution should be taken for patients with paroxysmal EEG activity.

TDCS of the motor and prefrontal cortices may have therapeutic potential in PD, but better stimulation parameters need to be established to make the technique clinically viable.

Preliminary analysis indicates that 50 Hz rTMS at an intensity of 90% RMT for up to 6 sec appears safe in patients with PD. The therapeutic efficacy has not yet been analyzed.

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